The University of Chicago

THE RELATION OF ESTRIN TO THE BASAL METABOLIC RATE

A DISSERTATION SUBMITTED TO THE FACULTY OF THE DIVISION OF THE BIOLOGICAL SCIENCES IN CANDIDACY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY
1939

By
GRACE WERTENBERGER

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INTRODUCTION

Though the effects of ovariectomy and the subsequent substitution therapy on the BMR have been extensively investigated, the results are by no means in complete agreement. The literature covering the effect of estrin upon the basal metabolic rate (reviewed by Allen, 1939; Zondek, 1930; v. Arvay and Meyer, 1932; Geisendorf, 1938; Geriola, 1938) is filled with contradictory evidence. The observations cover a wide range of preparations of estrogenic substances, dosages, and species. Reinvestigation of this relationship using some of the newer more highly purified preparations of estrin has seemed of value, especially with the increasing clinical use of these preparations in disturbances of hypo-ovarianism.

The first part of this work appeared two years ago (Collett, Smith, and Wertenberger, 1937) and covered a series of observations on castrate women before and after estrogen medication. It has been continued using castrate dogs, with observations before and after castration and during theelin injections. Some further observations on one of the human subjects previously observed are included.

METHOD

Metabolic determinations on dogs were made with the Benedict-Roth portable metabolism machine using the Kunde mask (Kunde et al., 1930) and under basal conditions as described by Kunde and Steinhaus (1926) in their study of basal metabolism of normal dogs. Two eight minute tests were run and the lower value used. Tests were excluded unless the duplicate agreed within 5 per cent. At the close of the test the rectal temperature and femoral pulse were recorded. The tests were run at the same time every day and 15 hours after feeding. This time is somewhat shorter than that advocated by Kunde (1926) who used an 18-20 hour interval. The dogs were turned into the runway, where defecation and urination occurred before being brought to the metabolism room.

Adult female dogs were selected in pairs for similarity

of build and weight. All dogs had been in this laboratory for at least one year and were thoroughly accustomed to the confinement of laboratory existence. They were free of snuffles and mange through the entire period. They were dewormed at the beginning of the experiment. They were kept in well-lighted, dry cages and allowed to exercise daily in the courtyard.

Each dog was fed 250 grams of cooked chopped meat, 250 grams of whole wheat or cracked wheat bread, and 100 grams of bone meal each day. This diet was supplemented after the first seven months with a vitamin concentrate (Squibb's Adex Tablet, 1/day). The diet and feeding time have been constant throughout the study.

After a preliminary control period of six months the animals were ovariectomized and hysterectomized under ether anesthesia. Recovery was rapid and uneventful. Metabolism observations were resumed after a recovery period of six weeks.

Estrin in the form of theelin in oily solution (Parke, Davis & Company) was used for substitution therapy and was given by intramuscular injection sixteen hours before a metabolism determination. The amount and dosage interval varied.

In the case of the human subject, determinations were made with a Krogh spirometer and checked by the open circuit apparatus and Haldane gas analysis. Consecutive tests on the same day with the Krogh and with the Haldane differ by less than 2 cc. O_2 per minute. A ten minute test was run after a rest period of thirty minutes, observing all the usual precautions concerning the basal condition. Pulse and temperature were recorded at the end of the test. Tests were run six days a week and medication given twelve hours before the observation. Normals were calculated by the Harris-Benedict standard.

RESULTS

The data on one human subject are presented in the following detailed protocol and summarized in Tables 1, 2, and 3.

The data on four dogs studied for six months before and two and a half years after castration are presented in Tables 4, 5, and 6. The effect of theelin substitution therapy, which varied in dosage, time interval between injections, and duration of

the period of medication, are also presented in Figures 2, 3, 4, and 5. All the basal metabolic data on dogs were analyzed statistically for significance of difference and the results are summarized in Table 6.

TABLE 1

EFFECT OF OVARIECTOMY ON BASAL METABOLIC RATE IN A WOMAN

Age Yrs.	Mos.	Time Since Operation	Weight lbs.	Date	BMR in cc. O_2 per min.	Per Cent of Harris-Benedict Standard
29	7		171	4/29	210	+ 0.6
32	4	1 month	150	1/30	...	....
34	1	22 months	180	10/33	200	-13.5
34	7	27 "	180	4/34	198	-12.5
35	1	33 "	180	10/34	182	-20.8
35	5	36 "	176	3/35	191	-15.0
36	5	48 "	186	2/36	203	-13.1
37	0	57 "	193	9/36	...	....
38	0	69 "	210	9/37	...	....
39	1	81 "	216	10/38	...	-18.5

TABLE 2

RANGE OF VARIATION IN BMR DURING CONTROL PERIODS IN CC. O_2 PER MINUTE FOR CASE A

Number of Tests	Range	Difference	Average	Per Cent Max. Spread
14	190 - 208	18	200	9.0
3	194 - 201	7	198	3.5
6	177 - 184	7	182	3.8
20	183 - 199	16	191	8.3

Case A: A white woman operated upon at thirty-two years of age, twenty-one months before the beginning of our experiments. She was in good health during the experimental periods except for the vasomotor disturbances characteristic of the menopause. In a series of tests made in connection with another problem at twenty-nine years of age, her metabolism was normal, plus 0.6 per cent by the Harris-Benedict Standard. Twenty-one months after operation the basal metabolism had fallen to -13.5 per cent. During the next two years it varied from -20.8 per cent to -13.1 per cent

TABLE 3

BASAL METABOLISM RATE IN PERCENTAGE OF INITIAL LEVEL AFTER CONSECUTIVE DOSES OF THEELIN IN CASE A

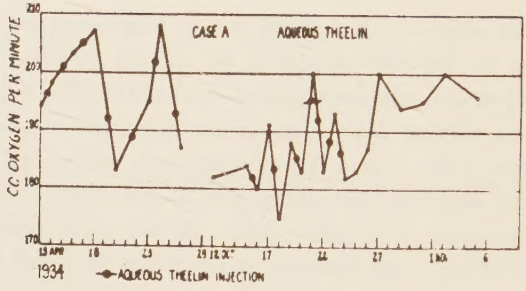
Prep.	Interval and Total Dosage IU	Range						Average					
		During	After Medication					During	After Medication				
			1 Wk.	2 Wk.	3 Wk.	4 Wk.	5 Wk.		1 Wk.	2 Wk.	3 Wk.	4 Wk.	5 Wk.
Aq. T EXP. I	6 in 15 da 300 RU	94-105	.....	.....	.....	.....	.....	101	...	...	...	...	...
C.L.	6 in 12 da	90-106	.....	.....	.....	.....	.....	100	...	...	...	...	...
Aq. T. EXP. II	6 in 9 da 300 RU	96-110	100-108	99-117	98-110	.....	.....	102	104	108	104	...	...
O. T.	6 in 6 da 1500 IU	97-102	96-103	98-102	.....	.....	.....	100	99	100	...	...	...
O. T.	6 in 6 da 3000 IU	101-110	93- 99	97-105	.....	.....	95-103	105	97	100	...	...	102
O. T. EXP. I (inj.)	6 in 6 da 6000 IU	89-102	93-103	100-101	.....	101-112	105-112	96	100	100	...	105	108
			6 Wk.	7 Wk.	8 Wk.				6 Wk.	7 Wk.	8 Wk.		
		.....	105-108	94-103	98-101	.....	.....	...	107	101	100	...	...
O. T. EXP. II	6 in 6 da 6000 IU	94-102	96-101	91- 98	.....	.....	.....	98	98	94	...	...	...

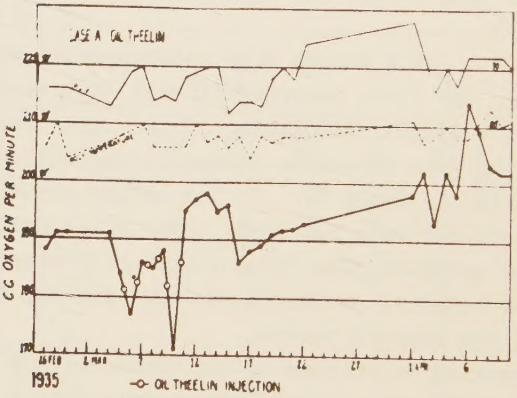
(Table 1). The absence of marked daily fluctuations considered as normal even in trained subjects is worthy of note. In the first control period, whose maximum variation was 9 per cent, 8 of the 14 tests varied less than 3 per cent and 4 consecutive tests were identical. In a longer control period of 20 tests one year later, the maximum variation was 8 per cent with half of the tests within a range of 4 per cent. In the next control period eleven months later, the maximum spread was 5.9 per cent with 7 of the 8 tests less than 4 per cent apart (Table 2 and Fig. 1, Graphs 1 and 2).

The effect of 2 series of 6 injections of aqueous theelin (50 R.U. each), the first covering fifteen days, and the second nine days, was a slight stimulation of the basal metabolism, the second series of more intensive dosage giving the greater rise (Table 3 and Fig. 1, Graph 1). In the latter series we followed the basal metabolism rate for three weeks after medication and found that the greatest rise (plus 8 per cent) came in the second week. The range of variation was much greater than that observed during the control period.

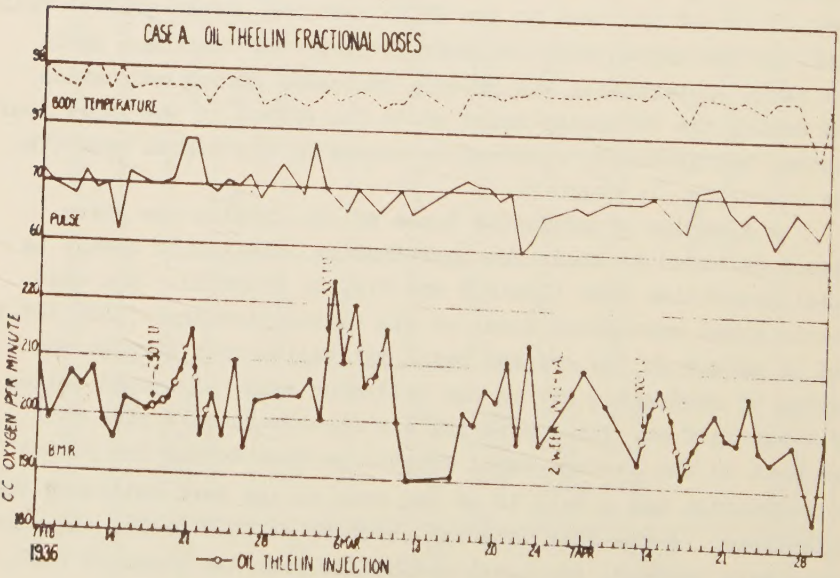
Consecutive injections of oil theelin (1000 I.U. per dose for six days) produced a fall to -4 per cent during the period of medication, with a gradual rise through the ensuing weeks to a peak of plus 8 per cent in the fifth week and then a gradual fall, until by the eighth week the initial level was reached. Again the range of variation was greatly increased during medication and during the following weeks while the effect of the injections lasted, but gradually returned to normal by the eighth week (Table 3 and Fig. 1, Graph 1).

A series of graduated doses of oil theelin was given Case A in order to study the quantitative relation of dosage to basal metabolism rate (Table 3 and Fig. 1, Graph 2). Six one-fourth cubic centimeter doses on six consecutive days (1500 I.U.) had no effect on the average basal metabolism rate through the period of medication nor in the following week. A second series of 6 one-half cc. doses covering six days produced a rise of 5 per cent in the average basal metabolism rate during the period of medication and a fall to -3 per cent in the week following the injections. A two-week interval occurred at this point, and when tests were resumed, the basal metabolism rate had risen to plus





Graph 1.



Graph 2.
Fig. 1.--Case A.

2 per cent. The last series of injections consisted of 1 cc. doses on six consecutive days and the basal metabolism rate fell to -2 per cent during medication and to -6 per cent two weeks later. The maximum variation during the first series did not exceed that observed during the control period. The next two series, however, produced the marked daily fluctuation and the increased range of variation previously noted after estrin medication. The observations should have been continued for at least two weeks longer in order to determine the full effect of the medication. This series is especially significant because it shows both stimulation and inhibition of the basal metabolism rate by estrin.

Menformon injections totaling 7200 M.U. in six days also raised the basal metabolism rate of Case A by 6.6 per cent during the period of medication, and, as in the case of theelin, produced a wider range of variation.

A day-to-day record of the number of hot flashes was not kept for Case A, but marked changes were noted. The hot flashes, which began in the third week after operation, were frequent and severe. A series of aqueous theelin injections did not alleviate them. The first relief was secured after a series of aqueous theelin followed by corpus luteum injections, but the effect was short-lived. We have generally observed that days of high basal metabolism rate after estrin medication are days of few vasomotor symptoms, but the rise in basal metabolism rate per se does not seem to be the only factor involved, for after thyroid medication the basal metabolism rate rose by 24 per cent and the vasomotor symptoms increased. Thyroid medication has repeatedly had this effect upon Case A. During the following year the hot flashes gradually disappeared spontaneously and the patient was free of them for about four months. A series of oil theelin injection begun at this time was accompanied by a sharp return of both hot flashes and headaches. As the dosage continued, these gradually faded and became almost negligible three weeks after medication. Insomnia and general nervousness responded better to theelin in oil than to the aqueous preparations. Since a prolonged effect is desired the oil preparations with their rate of absorption have a distinct advantage.

During the following two years the patient has steadily gained in weight until at six years and nine months after the op-

TABLE 4

EFFECT OF CASTRATION ON BODY WEIGHT AND BMR IN FEMALE DOGS

Time	Number of Tests				Weight in Kgs.			
	Dog				Dog			
	1	2	3	4	1	2	3	4
Control - 3 mos.	40	39	32	30	10.55	9.87	7.00	8.71
Operated - Mar. 9-12								
May: 2 mos. Post-op.	12	12	9	8	10.85	10.68	7.02	8.49
June: 3 " " "	8	7	5	5	11.59	11.44	7.61	8.86
Oct.: 7 " " "	8	9	6	5	11.99	12.00	8.18	9.32
Nov.: 8 " " "	11	12	8	7	12.08	12.01	8.30	9.09
Dec.: 9 " " "	8	8	7	6	11.90	12.25	8.52	9.17
Jan.: 10 " " "	5	1	3	6	11.62	12.44	8.41	9.06
Feb.: 11 " " "	16	14	19	18	11.73	12.95	8.41	8.98
Mar.: 12 " " "	13	13	12	12	11.90	13.43	8.58	8.98
Apr.: 13 " " "	11	11	11	10	11.76	13.27	8.67	8.95
Mar.: 24 " " "	12	9	8	11	12.01	11.60	9.46	10.63
Apr.: 25 " " "	5	6	8	7	12.50	11.50	9.66	11.05

TABLE 4 - Continued

Cals./Kg./hr.				Cals./Kg./24 hrs.				Percentage Change			
Dog				Dog				Dog			
1	2	3	4	1	2	3	4	1	2	3	4
2.23	1.68	2.35	3.76	53.62	40.42	56.42	90.14	.....	.....	.....	.....
2.42	1.75	2.18	3.42	58.01	42.00	52.22	82.45	+ 8.2	+ 3.9	- 7.0	- 8.2
2.27	1.07	2.08	4.51	54.36	25.68	49.92	108.28	+ 1.4	-36.0	-11.5	+20.2
2.28	2.22	3.32	4.98	67.94	53.18	77.18	119.61	+26.5	+31.0	+36.0	+32.7
3.07	2.26	3.78	4.14	73.70	54.14	90.91	99.32	+37.5	+33.9	+61.0	+10.1
2.11	1.29	2.15	2.36	50.52	30.86	51.60	56.70	- 5.7	-23.0	- 8.5	-34.4
1.82	1.30	1.73	1.90	43.73	31.22	41.64	45.61	-18.4	-22.9	-21.9	-49.3
1.89	1.55	2.36	2.11	45.46	37.08	56.59	50.64	-15.2	- 8.3	+ 0.7	-43.8
1.59	1.49	1.88	1.83	38.20	35.81	45.19	43.78	-28.7	-11.3	-19.8	-51.2
1.72	1.30	1.81	1.65	41.16	31.08	43.41	39.69	-23.2	-23.1	-22.8	-55.9
1.69	2.44	1.70	1.60	40.51	58.51	40.77	38.46	-24.4	+44.7	-27.7	-57.2
1.67	2.38	1.56	1.58	40.03	57.05	37.49	37.96	-25.3	+41.7	-33.6	-57.8

eration she weighed 216 pounds, a gain of 44.0 per cent over the second month post-operative level. The BMR, determined at this time in a hospital metabolic clinic before starting thyroid therapy for the obesity, was -18.5 per cent by Harris-Benedict Standard. The vasomotor symptoms have completely disappeared.

The effects of castration on the body weight and basal metabolic rate in the four dogs studied are summarized in Tables 4 and 5. The percentage change from normal is calculated on a basis of calories per Kg. per hour. The BMR showed no significant change in the first two months following castration and by the third month it had fallen significantly in Dogs 2 and 3, risen in Dog 4 and fallen slightly but well within the normal range in Dog 1. There was a sharp rise in all dogs during the eighth and ninth months and then a gradual fall until by the end of the first year all dogs had shown a significant decrease (Table 6). This decrease persisted through the second year in three animals but Dog 2, however, showed a sharp increase over her initial level. Her appetite which had always been good became voracious and, since the diet was kept constant, she began to lose weight. During July of the third year a watery diarrhea began which has stubbornly resisted all therapy.

The fluctuations of body temperature and pulse rate in general follow the BMR, with a depression during heavy dosage. This resembles the action noted in the previous work on humans (Collett, Smith, and Wertenberger, 1937).

TABLE 5

PERCENTAGE CHANGE IN BODY WEIGHT IN CASTRATE DOGS AND NORMAL CONTROL

Time	Castrated at End of Control Period								Unoperated Control	
	Dog 1		Dog 2		Dog 3		Dog 4		Dog 5	
	B.W. Kgs.	% Change	B.W. Kgs.	% Change	B.W. Kgs.	% Change	B.W. Kgs.	% Change	B.W. Kgs.	% Change
Control Period	10.55	.....	9.87	.....	7.00	.....	8.71	.....	9.31	.....
1 Year after castration	11.90	+12.7	13.43	+36.1	8.58	+22.5	8.98	+ 3.1	9.43	+1.2
2 Years after castration	12.50	+18.5	11.50	+14.1	9.66	+23.6	11.05	+26.8	10.00	+7.4

TABLE 6

SUMMARY OF SIGNIFICANCE OF DIFFERENCES BETWEEN PAIRS OF BASAL METABOLISM TESTS RECORDED AT VARIOUS STAGES OF ESTRIN THERAPY IN THREE DOGS, AS INDICATED BY STUDENT'S "T" TEST

Periods for Which Difference is Tested	Dog 3		Dog 4		Dog 2	
	No. of Obs.	"T"	No. of Obs.	"T"	No. of Obs.	"T"
1.(a)Pre-operative control.....	32	....	30	....	39	....
(b)Post-operative " (early)	57	2.51*	55	4.40*	64	4.28*
2.(a)Post-operative " (early)	57	....	55	....	64	....
(b) " " " (late)	23	2.63*	22	4.70*	24	2.13*
Fig. 1						
3.(a)Post-operative " (late)	23	....	22	....	24	....
(b)Oil Theelin #1, 5,000 IU in 10 days.....	9	2.46*	9	1.33	9	8.42*
4.(a)Oil Theelin #1.....	9	....	9	....	9	....
(b)Post Theelin #1 period.....	9	0.70	9	0.75	9	1.59
Fig. 2						
5.(a)Post Theelin #1 period.....	9	....	9	....	9	....
(b)Oil Theelin Inj. #2, 14,000 in 14 days.....	11	2.25*	11	1.04	9	3.92*
6.(a)Oil Theelin #2.....	11	....	..	....	..	....
(b)Post Theelin #2, 1 wk.....	6	3.97*	6	0.27	6	0.72
7.(a)Post Theelin #2, 1 wk.....	6	....	..	....	..	....
(b) " " ", 2nd and 3rd wks.....	11	2.13*	11	0.34	10	1.79
8.(a)Post Theelin #2 1st-3rd wks.	17	....	17	....	16	....
(b) " " " 6th-8th wks.	13	1.52	13	2.78*	13	3.64
9.(a) " " " 6th-8th wks.	13	....	13	....	13	....
(b)Oil " Inj. #3, 50,000 IU in 25 days.....	25	1.28	25	0.88	23	5.43*
Fig. 3						
10.(a)Oil Theelin Inj. #3.....	25	....	25	....	23	....
(b)Post " #3 1st-6th wks.	26	1.38	25	3.44*	25	1.49
11.(a) " " " " "	26	....	25	....	25	....
(b) " " #3, 5 1/2 mos. later	16	1.34	18	3.05*	15	8.88*
Fig. 4						
12.(a) " " " " " " "	16	....	18	....	15	....
(b) Oil " #4, 8,000 IU	12	0.14	12	4.60*	13	4.37*
13.(a)Oil Theelin Inj. #4..... Repetition of Series #1 1 year later	12	....	12	....	13	....
(b)Post Theelin #4.....	10	0.26	10	0.97	10	2.57*

*Indicates that the value of T is at or above the 5% level of significance.

DISCUSSION

The results presented agree with most of those previously presented in indicating that castration lowers the basal metabolic rate. The fall is not a sharp one following immediately upon operation but develops rather slowly, showing marked fluctuations during the first year. Ptaszek (1929) who also observed this fluctuation called this rise and return to and above the original control level the compensatory period, believing it to be due to compensatory stimulation of the BMR by the thyroid to overcome the initial fall after operation. He finds that the metabolism finally returns to a permanent level significantly below that of the control. His values range from -34 per cent to a -57 per cent for female dogs. It also agrees with the findings of Murlin and Bailey (1917) who repeated and confirmed the early work of Loewy and Richter (1899). Lüthji (1902) however, was unable to demonstrate any significant difference in CO_2 output of two castrate female dogs as compared to that of two normals.

In the case of the human patient, the normal level of the BMR two years previous to operation indicates that there was normal thyroid function. This diminution in the BMR following castration confirms the bulk of the evidence presented for women but does not agree with King's (1926) work on a large series of cases of surgical and natural menopause in which he found the basal rate of such women close to the normal level. We feel, however, that the pre-operative BMR value obtained as a control in a previous work and the prolonged observations on the post-operative course of the BMR makes these data on Case A, unique and almost a laboratory experimental case. Individual variations during the long periods did not vary more than 9 per cent.

The question of castrate obesity has been extensively discussed (Geriola, 1938; Korenchevsky, 1925; Sandberg, Perla, and Holly, 1939). Korenchevsky points out that there are "thin" castrates and "fat" castrates and in the latter the BMR tends to show a significant diminution. It would seem that the cases here reported belonged to the latter class. Case A whose dietary habits did not change was living at the same place for one year pre-operative and four years post-operative. The weight gain is well

over that of normal expectation.

While the weight gain in the dogs was not as marked as that in Case A, their diet was constant and environmental conditions, designed to maintain "normal muscle tone" and vigor as set forth by Kunde and Steinhaus (1926) were carefully controlled. Two control dogs kept under same conditions gained 1.2 per cent and 3.9 per cent (Tables 4 and 5). However, the weight gain was more rapid and greater during the second year in the dogs. Sandberg, Perla, and Holly (1939) showed that weight curves in female rats castrated after puberty show a gain over the control in spite of the fact that their food intake expressed in grams/100 grams of body weight was less. Zondek (1935) in his discussion of castration obesity regards it as a genuine metabolic form of obesity and goes on to say, "in my opinion there can be no doubt as to the accuracy of Loewy and Richter's results which I have confirmed experimentally, and observed clinically in women after castration."

Oil theelin injections gave varying effects on the BMR. In Dog 2 the basal rose significantly during light doses of estrin in both Series #1 and Series #4 carried out one year later (Figs. 2 and 5). With intensive dosage (Series #2 and #3, 14,000 I.U. in 14 days; and 50,000 I.U. in 25 days, respectively) the basal was significantly depressed during the latter part of the injection period as the hormone concentration increased and rose after cessation of medication gradually returning to normal. The rise above the control level during the latter part of this rest period is within normal limits (Figs. 3 and 4). In this response to light and heavy estrin dosage this dog repeats the effects observed on Case A and in human castrates (reported in an earlier paper, Collett, Smith, and Wertenberger, 1937). Theelin effects on the other dogs, however, varied, Dogs 3 and 4 showing significant responses (Table 6). The tendency is toward a slight rise with light doses and a depression with heavy doses of the hormone, the BMR returning to normal and rising slightly above normal after medication. The depression appears more consistently than the rise; Kunde et al. (1930) reports basals near the lower limits of the range of normal variation, average of all tests showing a 2 per cent fall below controls, with injections of ovarian extract in the normal female dog.

The mechanism by which estrin affects the basal metabolism

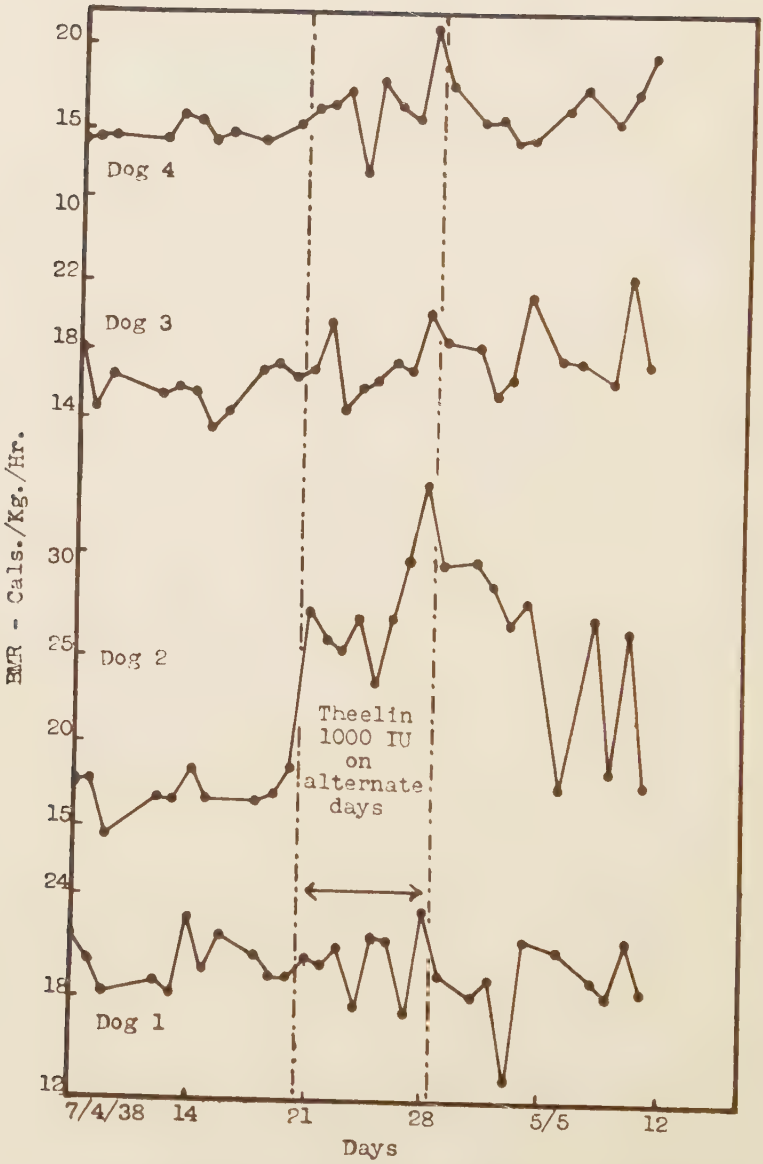


Fig. 2.--The Effect of Theelin on the BMR of Castrate Dogs. Series #1; Total - 5,000 IU.

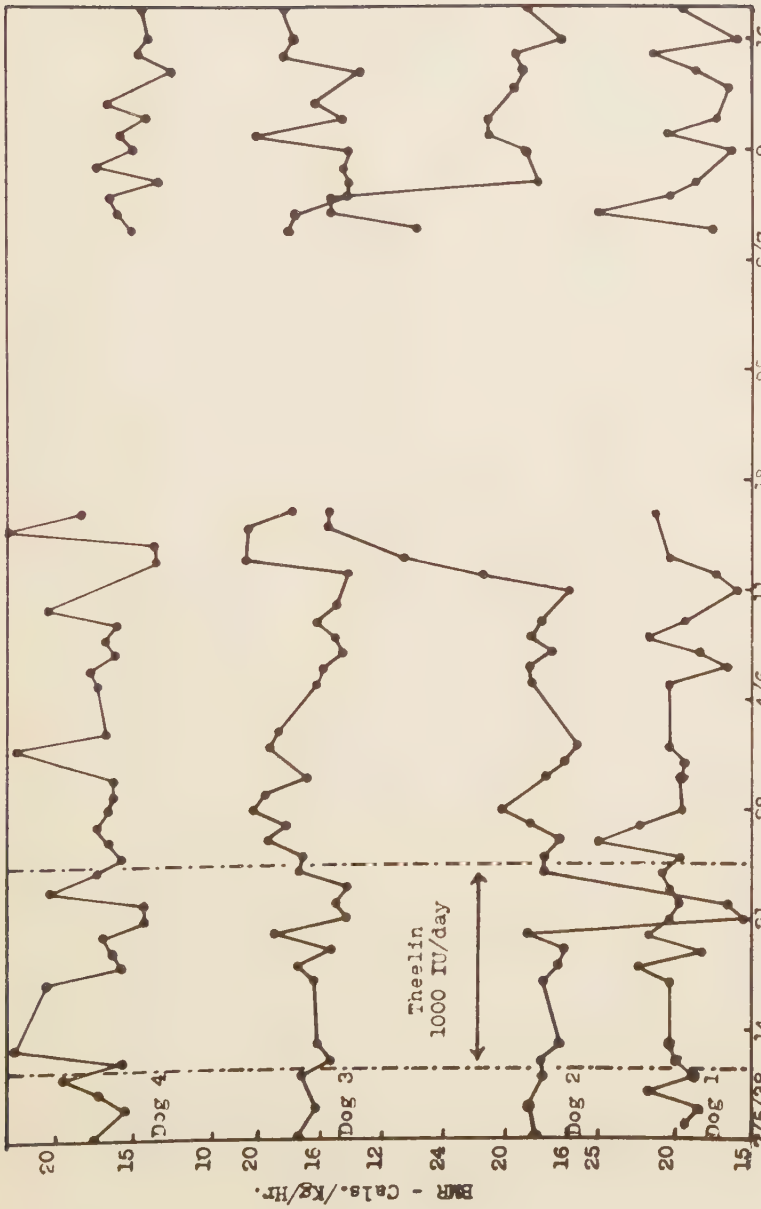


Fig. 3.--The Effect of Theelin on the BMR of Castrate Dogs. Series #2; Total - 14,000 IU.

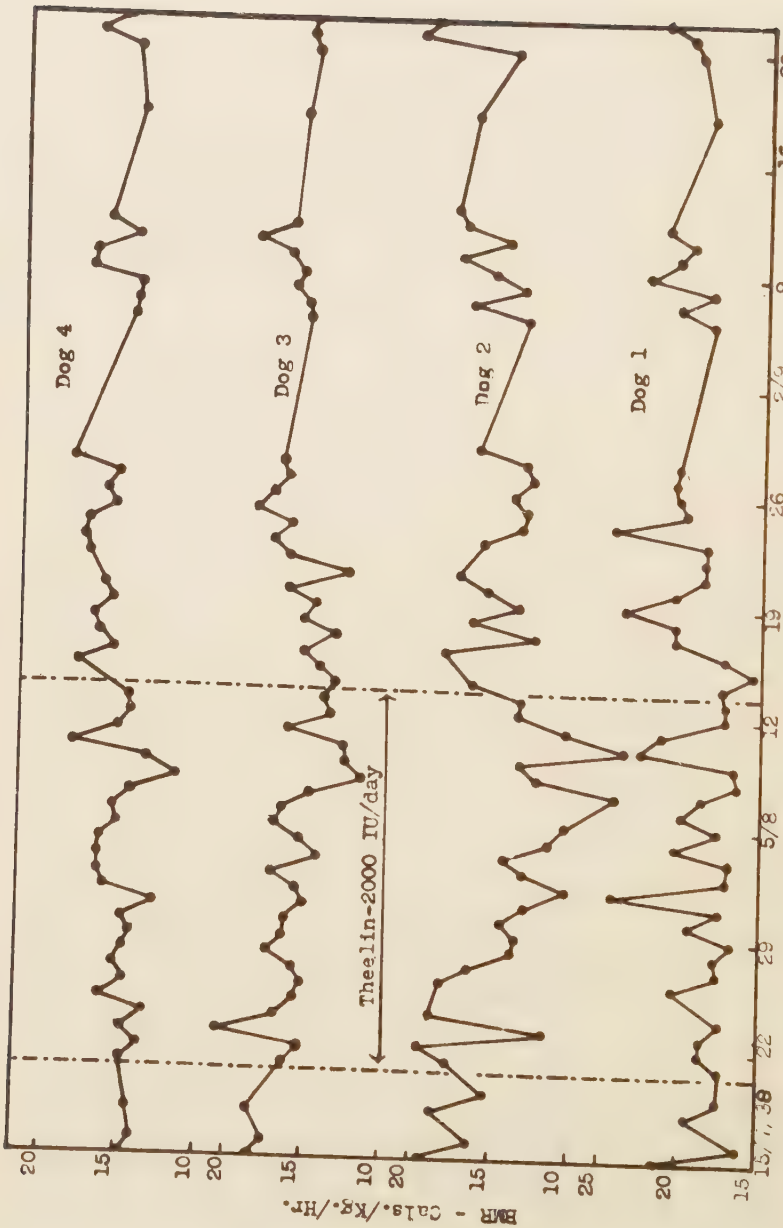


Fig. 4.--The Effect of Theelin on the BMR of Castrate Dogs. Series #3; Total - 50,000 IU.

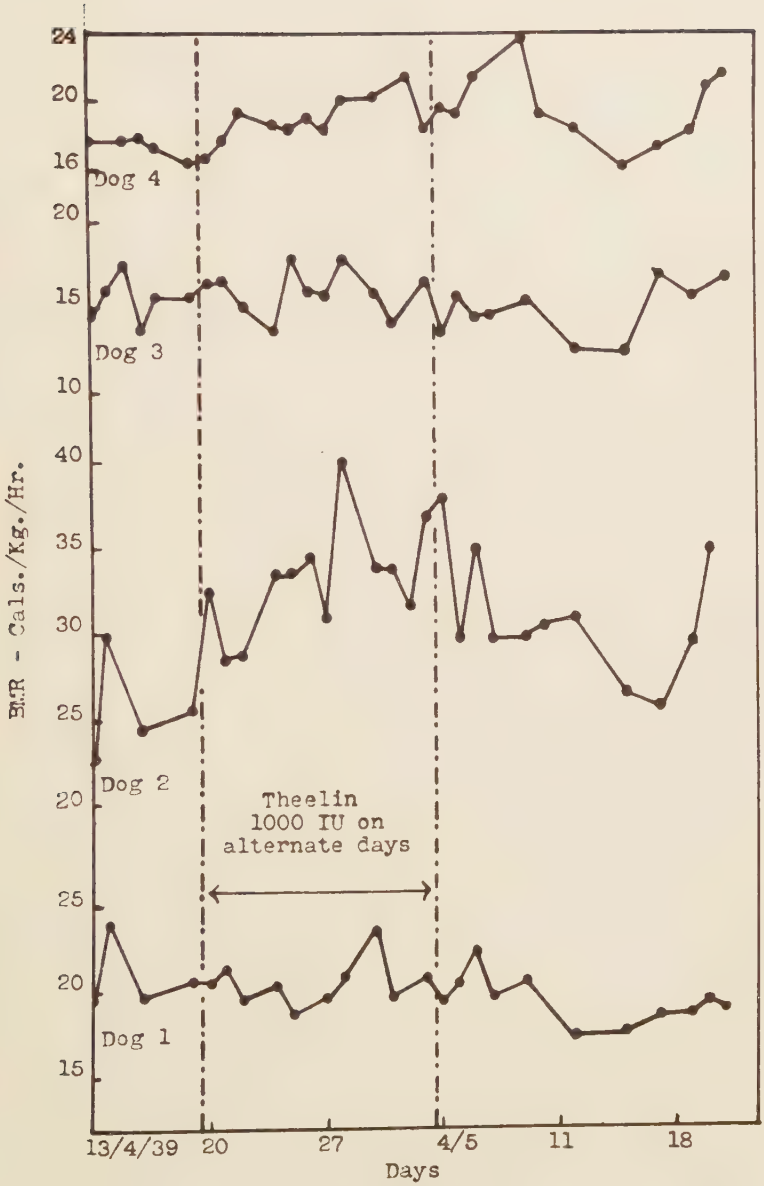


Fig. 5.--The Effect of Theelin on the BMR of Castrate Dogs. Series #4; Total - 8,000 IU.

rate is not clear. Anselmino (1934) and Pratt (1936) suggest a special thyrotropic hormone of the ovary. Geisendorf (1938) in an extensive review on the subject stresses the fact that metabolism is stimulated only when preparations of the whole ovary are used, not the pure follicular hormone. He speaks of the ovary as containing follicular hormone, lutein hormone, and a metabolic stimulating hormone and stresses the possibility of interstitial glands. He points out that while estrin is growth stimulating and raises the metabolism of certain tissues (uterus, vagina, and mammae), it does not raise the "fundamental basal metabolic rate." This is brought about by whole ovary with its metabolic hormone.

Verzar and v. Arvay (1931) report that menformon and theelin cause a rise of 10-20 per cent in the BMR of castrate female rats, but have no effect on normal or castrate males. This effect persists in castrate females even after thyroidectomy but not after hysterectomy. They attribute this rise to increased work of the uterus which they estimate to be from 500-1000 per cent.

Grumbrecht and Loeser (1938) in a very interesting piece of work point out that the histological picture of the thyroid after castration is one of hypo-activity in the rat, due to a decreased response of the gland to thyrotropic stimulation. They maintain that hysterectomy or tying the tubes will produce the same result, since the ovarian hormone also enters the blood by passing from the peritoneal sac down the tubes into the uterus. They show that estrin will not prevent castration atrophy of the thyroid in the castrate hysterectomized rat, but will in the castrate rat receiving intrauterine injections. The authors advance several hypotheses for this action, namely, that estrin is chemically changed on its way through the uterus to become thyrotropic or that it stimulates the uterus to secrete a thyrotropic factor, or that estrin after going through the uterus is capable of sensitizing the thyroid to anterior pituitary thyrotropic hormone.

Case A of this series, however, was totally hysterectomized and gave significant rises in BMR with theelin injections.

The bulk of the experimental evidence points to an ovarian-hypophyseal-thyroid relationship with the hypophysis as an intermediary because of its thyrotropic action. The reciprocal relationship between the anterior pituitary and the ovary is well es-

tablished. Moore and Price (1932) found the secretion of both gonadotropic and growth hormones inhibited by estrin. The increase in the gonadotropic power and the hyperplasia of the A. P. has been demonstrated in different species. Lane (1935) found that small estrin doses stimulate, while heavier dosages inhibit, the production of gonadotropic hormone. This inhibition under heavy estrin dosage is explained by Halpern and d'Amour (1936) as being due to an overstimulation of the pituitary which brings about a period of overgrowth at the expense of secretory activity.

The close relationship existing between the pituitary, thyroid and ovary has been clearly established both experimentally and clinically. Kippen and Loeb (1936) found that histologic evidence of thyroid stimulation occurred during the first week after gonadectomy, but that this effect soon disappeared and thyroid activity then fell below normal. Andersen and Kennedy (1933) have described an atrophy of both adrenals and thyroid after ovariectomy, and a temporary increase in pituitary weight. According to Zwecker (1936) the "castration cells" of the pituitary do not produce the thyrotropic hormone, for special cells which she calls "thyroidectomy cells" appear in several species alongside the castration cells after thyroidectomy. She considers the reaction sufficiently different to suggest that the basophils of the anterior lobe of the pituitary are of two kinds, namely, those reacting to thyroidectomy and those reacting to gonadectomy. She also reports a decrease in the number of acidophils, sometimes in a striking degree, the controlling factor being unknown.

Nelson and Hickman (1939) repeating this work, injected estrin into the thyroidectomized castrates to prevent the castration changes which occur in the pituitary. The untreated animals showed the two types of cells described by Zwecker, but the estrin injections completely, or almost completely in the cases of delayed treatment, corrected both types of changes. The marked decrease in granulated acidophils, however, was apparently unaffected by estrin. The authors offer this as evidence against the hypothesis that the basophils which react differently to the two operations are two different types.

The antithyroidal effect of estrin has been employed clinically to treat various conditions of hyperactivity of the thyroid with positive results evidenced by a fall in the BMR and improve-

ment of circulatory and nervous symptoms (Starr and Patton, 1935; Zain, 1937; Geriola, 1938). Sherwood and Bowers (1936) reported a fall in the BMR of hyperthyroid rats of 10-54 per cent following the injection of theelin or amniolin. Following thyroidectomy amniolin had no effect on the BMR (Sherwood, Wilson, and Boneta, 1937). Gessler (1936) reported decreases in BMR of normal and hyperthyroid guinea pigs following estrin injections. Danforth, Green, and Ivy (1937) report estrogen as without effect on metabolism of normal rats but preventing in part the calorigenic effect of thyroid when the two hormones were given simultaneously.

It has been shown that the basal metabolism of normal women varies with the different phases of the menstrual cycle (reviewed by Hitchcock and Wardwell, 1929; Rubenstein, 1937) with a fall at the midpoint of the cycle and a peak in the week preceding and the week after the menstrual period. These two high points correspond to times in the cycle when the corpus luteum and the follicle appear to be very active. Women with faulty ovarian function are likely to have a low metabolic rate (Litzenberg, 1929; Randall, 1934; Thurman and Thompson, 1930).

Collip and his co-workers (1938) have recently announced the isolation of a specific metabolic principle of the pituitary other than thyrotropic hormones which has a profound metabolic effect giving an average increase of plus 28.7 per cent in the BMR.

These data suggest that the mechanism might be either direct stimulation of all body cells which would include thyroid and this increased thyroid hormone would further stimulate metabolism, or indirect stimulation or inhibition of the thyroid by way of the pituitary.

The bulk of the evidence is toward the theory of indirect control of general metabolism by indirect control of the thyroid by way of the pituitary.

If the inhibition were exercised directly on the metabolic processes in the cells, then thyroidectomy should not change the decrease in the BMR observed in rats with estrin injection. This is not supported experimentally (Sherwood, Wilson, and Boneta, 1937). But if the inhibition is by way of hypophyses over thyroid, then it seems reasonable to expect that, coincident with fluctuations in the pituitary activity due to ovarian control, we have fluctuations of thyroid activity which are reflected in meta-

bolic rate changes. Whether a rise or a fall in the BMR after estrin will then depend upon the size of the dose and the duration of the treatment. Deanesly and Parkes (1937) point out that the effectiveness of the response to sex hormones, both androgens and estrogens, is profoundly influenced by the subdivision of the dose, the nature of the solvent, addition of fatty substances to the medium, and route of administration. This is a timely warning and should be borne in mind when comparing results from different laboratories.

Winkler (1938) in a critical review based on personal observations and those of others advances the hypothesis that the three internal secreting bodies, hypophysis, thyroid, and adrenals influence it in part directly and in part through the peripheral and central autonomic nervous system. This action is seldom individual and the harmonizing and balancing of these several factors is brought about by a BMR regulating center located in the midbrain.

The relief of nervous symptoms which appear with the menopausal syndrome generally parallels a rising metabolism but that increased metabolism, per se, is not the only factor involved was shown in Case A when a 24 per cent increase in BMR following thyroid administration was accompanied by severe vasomotor symptoms: This increased irritability of the sympathetic nervous system was probably an expression of adrenalin hypersensitivity, since it is well known that thyroid hormone sensitizes the body cells to the action of adrenalin (Marine, 1935). It is probable that relief of the nervous symptoms is due to the direct effect of the ovarian hormone on the pituitary and the adrenals; Hannan's (1928) theory points to action upon the adrenals whose unbalanced behavior resulting from a withdrawal of the ovarian hormone brings about an increased tonus of the sympathetic nervous system.

CONCLUSIONS

I. Castration and hysterectomy lowered the BMR of four dogs and one woman to a level varying from -12.5 to -20.8 per cent by the Harris-Benedict Standard in the case of the woman; and -23.1 to a -57.8 per cent in the dogs.

II. This decrease in the BMR is accompanied by an increase

in body weight.

III. Estrin in the form of oil theelin affects the basal metabolic rate. Heavy doses produce a fall during the administration of the hormone which is succeeded by a rise in the BMR, small doses tend to stimulate the BMR.

IV. The effect of estrin on the BMR of dogs is not consistent in this series, two dogs showing responses that fall within the range of normal variation though on the lower limits, and two dogs showing statistically significant responses.

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